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Candida Infective Endocarditis

John W. Baddley, MD[1,2], **Daniel K. Benjamin Jr., MD, MPH,PhD**[3], **Mukesh Patel, MD**[1,2], **José Miró, MD, PhD**[4], **Eugene Athan, MD**[5], **Bruno Barsic, MD, PhD**[6], **Emilio Bouza, MD,PhD**[7], **Liliana Clara, MD**[8], **Tom Elliott, PhD**[9], **Zeina Kanafani, MD, MS**[10], **John Klein, MD**[11], **Stamatios Lerakis, MD**[12], **Donald Levine, MD**[13], **Denis Spelman, MD**[14], **Ethan Rubinstein, MD, LL.B**[15], **Pilar Tornos, MD**[16], **Arthur J. Morris, MD**[17], **Paul Pappas, MS**[18], **Vance G. Fowler Jr, MD, MHS**[3], **Vivian H. Chu, MD, MHS**[3], and **Christopher Cabell, MD, MHS [on behalf of for the International Collaboration on Endocarditis-Prospective Cohort Study Group]**[3]

[1]Department of Medicine, Division of Infectious Diseases, University of Alabama at Birmingham, 1900 University Boulevard, 229 THT, Birmingham, Alabama, USA, 35294-0006 [2]Department of Medicine, Infectious Diseases Section, Birmingham Veterans Administration Medical Center, 700 19th Street South, Birmingham, Alabama, USA, 35233 [3]Department of Medicine, Duke University Medical Center, PO Box 1799, Durham, North Carolina, USA, 27715 [4]Department of Medicine, Infectious Disease Service, Institut d'Investigacions Biomediques August Pi i Sunyer-Hospital Clinic, University of Barcelona, Villarroel, 170, Barcelona, Spain, 08036 [5]Department of Infectious Diseases, Barwon Health, The Geelong Hospital, PO Box 281, Geelong, Victoria, Australia, 3220 [6]Department of Infectious Diseases, University Hospital for Infectious Diseases, Mirogojska 8, Zagreb, Croatia [7]Department of Medical Microbiology, Hospital General Universitario Gregorio Marañón, Dr. Esquerdo 46, Madrid, Spain, 28007 [8]Hospital Italiano, Buenos Aires, Argentina [9]Department of Clinical Microbiology and Infection Control, Queen Elizabeth Hospital, Edgbaston, Birmingham, United Kingdom, B15 2TH [10]Department of Medicine, American University of Beirut

Corresponding Author: John W. Baddley, M.D., University of Alabama at Birmingham, Department of Medicine, Division of Infectious Diseases, 1900 University Boulevard, 229 Tinsley Harrison Tower, Birmingham, AL 35294-0006.

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Medical Center, Beirut, Lebanon [11]Department of Microbiology, St. Thomas' Hospital, 5th Floor North Wing, Lambeth Palace Road, London, United Kingdom, SE1 7EH [12]Department of Medicine, Emory University, 1365A Clifton Road, NE, Atlanta, Georgia, USA, 30322 [13]Department of Medicine, Wayne State University, 4201 St. Antoine Boulevard, Detroit, Michigan, USA, 48201 [14]Department of Microbiology, The Alfred Hospital, Commercial Road, Melbourne, Victoria, Australia, 3004 [15]Department of Medicine, Section of Infectious Diseases, University of Manitoba, 543-730 William Avenue, Winnipeg, Manitoba, Canada, R3E0W3 [16]Department of Cardiology, Hospital Universitari Vall d'Hebron, P Vall d'Hebron 119-129, Barcelona, Spain, 08035 [17]Department of Microbiology, Auckland City Hospital, Grafton, Auckland, New Zealand [18]Outcomes Research and Assessment Group, Duke Clinical Research Institute, Durham, North Carolina, USA, 17969 [19]ICE-PCS Study Group Investigators are Listed in the Appendix

Abstract

Purpose—*Candida* infective endocarditis (IE) is uncommon but often fatal. Most epidemiologic data are derived from small case series or case reports. This study was conducted to explore epidemiology, treatment patterns, and outcomes of patients with Candida IE.

Methods—We compared 33 *Candida* IE cases to 2716 patients with non-fungal IE in the International Collaboration on Endocarditis - Prospective Cohort Study. Patients were enrolled and data collected from June 2000 until August 2005.

Results—Patients with *Candida* IE were more likely to have prosthetic valves ($p<0.001$), short term indwelling catheters ($p<0.0001$), and have healthcare-associated infection ($p<0.001$). Reasons for surgery differed between the two groups: myocardial abscess (46.7% vs. 22.2% $p=0.026$) and persistent positive blood cultures (33.3% vs. 9.9%, $p=0.003$) were more common among those with *Candida* IE. Mortality at discharge was higher in patients with *Candida* IE (30.3%) when compared to non-fungal cases (17%, $p=0.046$). Among *Candida* patients, mortality was similar in patients who received combination surgical and antifungal therapy versus antifungal therapy alone (33.3% vs. 27.8%, $p=0.26$). New antifungal drugs, particularly echinocandins, were used frequently.

Conclusions—These multi-center data suggest distinct epidemiologic features of *Candida* IE when compared to non-fungal cases. Indications for surgical intervention are different and mortality is increased. Newer antifungal treatment options are increasingly used. Large, multi-center studies are needed to help better define *Candida* IE.

Introduction

Candida infective endocarditis (IE) is a rare and poorly understood complication of fungemia. Although *Candida* IE has been regarded traditionally as an uncommon infection, rates of fungemia have increased by as much as 128% in recent years, leaving a growing number of patients at risk for this complication[1]. Despite aggressive antifungal and surgical therapy, mortality approaches 80% in some series and a better understanding of this infection is needed [2–4].

Because of the rarity of candidal IE at any single institution, the epidemiology, prognosis, and optimal therapy of *Candida* IE are poorly defined, and treatment guidelines are derived mostly from single-site case series and case reports [3–6]. The recommended treatment of *Candida* IE is an amphotericin B-based regimen plus surgical intervention, often followed by long-term fluconazole for suppression[5]. However, because of the availability of safe, effective drugs for invasive candidiasis, emerging azole resistance, and high mortality, alternative drugs are now being increasingly used for *Candida* IE [7–14].

In the current investigation, we used a contemporary, prospective, international, multi-center cohort of patients with definite endocarditis to better evaluate the clinical characteristics, current antifungal treatment practices, and outcome of patients with *Candida* IE. Moreover, we compare and contrast *Candida* IE cases with non-fungal cases in order to highlight differences in epidemiology and outcomes.

Materials and Methods

Study Population

Patient data are derived from the International Collaboration of Endocarditis Prospective Cohort Study (ICE-PCS), a multi-national database of prospective cases of endocarditis. Details of the ICE-PCS have been described previously [15–17]. From June 2000 to August 2005, there were 2760 cases of definite IE contributed by sixty-one centers in 28 countries. Of the 2760 cases of definite IE, there were 33 cases due to Candida *spp*. All cases were classified as definite IE based on revised Duke criteria [18] and all cases were verified by the coordinating center (Duke University Medical Center). Fungal IE cases caused by organisms other than *Candida* (11 cases) were excluded from analysis. From each enrolled patient, data were collected from the index hospitalization and entered using an internet-based system. Data collected included demographics, symptoms associated with IE, underlying medical conditions, predisposing factors, clinical signs and symptoms, antifungal therapy, echocardiographic findings, associated complications and outcomes (stroke, embolic events, heart failure, intracardiac abscesses, persistently positive blood cultures, and death). Healthcare-associated IE was defined as either nosocomial infection or non-nosocomial healthcare-related infection. Nosocomial infection was defined as IE developing in a patient hospitalized for more than 48 hours before the onset of signs/symptoms consistent with IE. Death was determined at time of hospital discharge. Data on longer-term mortality was not collected.

Statistical Methods

Categorical variables were represented as frequencies and percentages of the specified group. The associations between clinical characteristics and *Candida* IE were measured using the Wilcoxon rank sum test for continuous variables and Chi square or Fisher's exact methods for categorical variables. For all tests, statistical significance was determined at the 0.05 level. All statistical analyses were performed using SAS software (version 9.1, SAS Institute, Cary, NC).

Results

Patient characteristics

Of the 2,749 patients with definite IE, 33 (1.2%) were *Candida* IE cases. The mean age of patients with *Candida* IE was 54.9 years. Patient characteristics including diabetes, renal disease, malignancy, intravenous drug use, and congenital heart disease were similar between the two groups (Table 1). Patients with *Candida* IE were less likely to be male (51.5% vs. 67.9%, p=0.04), more frequently had previous endocarditis (21.2% vs. 7.8%, p=0.005), and were more likely to have short term indwelling catheters (21.2% vs. 4.4%, p<0.0001). Among patients who had an invasive procedure within 60 days prior to onset of symptoms, CABG was more common among Candida IE patients (22.2% vs. 3.7%, p=0.007). Prosthetic valve IE was more common in *Candida* patients (48.8% vs. 19.6%, p=0.005), and *Candida* IE patients were more likely to have the infection classified as being healthcare-related (51.5% vs. 25.8%, p=0.0009).

Clinical findings

Of patients with any IE etiology, most (75%; 2068/2749) experienced the first clinical manifestation less than one month before presentation, and timing of IE manifestations was similar between the two groups. The most common clinical manifestations among all patients were fever (79.5%; 2170/2728), new murmur (47.9%; 1053/2198), hematuria (22.1%; 607/2737), pulmonary edema (22.3%; 556/2491), and evidence of a vascular embolic event (15.9%; 435/2728). Overall, there was little difference of symptoms and signs at presentation between the *Candida* and non-fungal IE groups (Table 2). Thirteen-hundred sixteen (47.9%) of 2749 patients had surgery for endocarditis, and this was not different for the two groups.

Candida IE patients were more likely to have surgery indicated because of embolization (40% vs. 19.8%, p=0.054), persistent fungemia (33% vs. 9.9%, p=0.003), and myocardial abscess (46.7% vs. 22.2% p=0.026). By contrast, surgery for the indications of congestive heart failure (42.6% vs 13.3%, p=0.02) and valvular regurgitation (68% vs 40%, p=0.018) were more common in patients with non-fungal IE.

Complications

Congestive heart failure, systemic embolization after presentation, and stroke were common but similar in occurrence in the two groups. *Candida* IE was associated with persistently positive blood cultures (39.4% vs. 8.8%, p<0.001) (Table 3). Mortality at time of discharge was higher among *Candida* IE patients than non-fungal IE patients (30.3% vs 17%, p=0.046). This mortality difference was more pronounced among those patients who had surgery for this episode of IE (33.3% vs. 13.8%, p=0.03). Among 15 *Candida* IE patients who underwent surgical intervention for this episode of endocarditis, mortality at discharge was similar to *Candida* IE patients who did not have surgery (33.3% vs. 27.8%, p=0.26). Those patients who underwent surgical intervention were more likely to have previous IE (40% vs. 5.7%; p=0.016), previous surgery for IE (33.3% vs. 5.6%; p=0.009), paravalvular complications on ECHO (46.7% vs. 11.1%; p=0.015), and systemic embolization (46.7% vs. 16.7%; p=0.04) when compared with patients with *Candida* IE who were not treated with surgical intervention.

Organisms and Antifungal Treatment—Among the 33 patients with *Candida* IE, 16 (48%) were caused by *C. albicans*, 7 (21%) *C. parapsilosis*, 5 (15%) *C. glabrata*, and 3 (9%) *C. tropicalis*. Two (6%) isolates were not fully speciated. Treatment data were available for 27(82%) of 33 patients (Table 4). The most common antifungal agent used was amphotericin B (AmB), either conventional AMB (13/27; 48.1%) or a lipid formulation (3/27; 11.1%). Fluconazole was used in 12 (44.4%) of 27 patients. Primary therapy with fluconazole was used in 6 (54.5%) of 11 patients with complete fluconazole treatment data available. Ten patients (37%) received treatment with the newer antifungal agents caspofungin or voriconazole. Among patients who received single drug therapy, death occurred in 6(40%) of 15 patients; death occurred in 2(25%) of 8 who received sequential therapy. In only two cases combination therapy was used and both patients were alive at discharge. Two (20%) of 10 people who received newer therapies (caspofungin or voriconazole) died.

Discussion

Candida IE is an uncommon but frequently fatal infection [3,4,6]. A better understanding of the epidemiology, associated risk factors, and treatment methods is needed but difficult to obtain because of the rarity of cases and lack of large prospective cohorts. We compared contemporary clinically well-characterized cases of candidal IE to non-fungal IE cases registered as part of a large, multi-center, prospective dataset to better understand *Candida* IE. This analysis revealed several important observations regarding predisposing conditions, clinical findings, and treatment modalities.

Important risk factors or predisposing conditions for fungal endocarditis have been reported in recent, extensive reviews, and the most frequently reported are previous surgery, vascular lines, antibiotic use, underlying heart disease, prosthetic valves, and immunocompromising conditions [2–4,6]. We found similar predisposing conditions and noted several distinct differences among *Candida* and non-fungal IE cases. First, coronary artery bypass grafting (CABG) and prosthetic valve IE were significantly more common in *Candida* patients. An increase in previous CABG among *Candida* IE patients could be explained by CABG being performed in association with prosthetic valve surgery. Second, healthcare-associated IE was more common among patients with *Candida* IE. The increase in hospital-acquired *Candida* IE in general is consistent with recent data describing *Candida* as an emerging nosocomial bloodstream pathogen over the past decade[19].

The clinical findings and presentation of patients with *Candida* and non-fungal IE are very similar, as has been previously described [6]. The most important exceptions discovered in our review are related to indications for cardiac surgery. Of patients who had surgery during this episode of IE, those with *Candida* IE were more likely to have surgery based on the finding of myocardial abscess, or persistently positive blood cultures. Non-fungal cases more commonly had heart failure or valvular insufficiency as a reason for surgery.

There were few differences in complications and outcomes in the two groups except mortality. *Candida* IE mortality has been reported to be up to 80% in previous reviews[2–4,6], but variability in data collection and description of individual cases makes it difficult to determine an appropriate risk of death. Ellis and colleagues in a recent review demonstrated that the crude survival of patients with fungal endocarditis had increased over the past twenty years, from 14% before 1970 to 41% in the period of 1991–1995 [3]. Possible reasons for this improved survival were attributed to better echocardiographic techniques, earlier diagnosis of endocarditis, or better supportive care of ill patients [3]. Nearly one-third of patients in our series died during hospitalization, with mortality significantly greater than non-fungal cases. The mortality among patients with *Candida* IE in our series is surprisingly less than reported in previous reviews, but may be due to a multitude of factors. Diagnostic and treatment modalities have improved in the past decade, but likely cannot account for such a difference in survival. The inclusion of *Candida* cases only, which often have better survival compared to other fungal causes[3,4]; and the survival end-point defined at hospital discharge (compared to literature reviews where follow-up data were available for up to several years) may reflect the lower mortality in this series [3]. Finally, the use of newer antifungal therapies such as the echinocandins and lipid preparations of amphotericin B, not included in previous reviews because of lack of availability, may have an impact on outcomes and warrant further evaluation.

The traditional antifungal treatment of *Candida* IE is amphotericin B (6–8 weeks), often followed by fluconazole as suppression because of frequent relapse [5,6]. In addition, surgical intervention with valve replacement is generally recommended in most cases. The combination of antifungal and surgical therapy is purported to be more beneficial than antifungal therapy alone, although controlled studies have not been performed for confirmation [3,4,20]. In this cohort, surgical therapy was not associated with increased survival compared to antifungal therapy alone. It is encouraging that patients who did not receive surgical therapy fared relatively well; however, we speculate that the lack of a significant difference in the groups may reflect a combination of factors including increased morbidity and complications at presentation among patients who underwent surgery. Patients who underwent surgical intervention were more likely to have previous IE, previous surgery for IE, paravalvular complications on ECHO and systemic embolization. Although these may be important differences that influenced risk of death, with the limited number of patients evaluated it is difficult to draw conclusions with respect to the appropriate management.

In this cohort, an amphotericin B preparation was the most frequent drug used. Fluconazole was second most common, and was used either for primary or sequential therapy. Sequential therapy was frequently employed, and mortality in this group was lower than in patients who received a single agent. This probably results from selecting a subset of patients that lived long enough to "step down" to azole therapy. Length of therapy and dosages were not captured, so appropriate comparisons cannot be made. An important obstacle in successful antifungal therapy of *Candida* IE has been adverse events associated with prolonged amphotericin B administration. With the approval of new antifungal agents in the past several years, specifically echinocandins and newer azoles, questions have arisen about the role of these agents for the treatment of *Candida* IE. The echinocandins and voriconazole have shown efficacy and safety for the treatment of invasive candidiasis and candidemia [21,22]; however, data on use in endocarditis is limited to case reports[7–14]. Although some clinical success has been documented, selection bias may be present, and determinations of efficacy cannot be made. Our series reflects a shift in the treatment of *Candida* IE. Greater than one-third of patients received newer antifungal agents, particularly the echinocandin, caspofungin, and mortality among these patients (20%) was similar to other groups. Adverse events from drug use and isolate susceptibilities were not captured in the database, so the reasons for the use of these drugs are unclear.

Although an important aspect of this dataset is its overall size, and this represents the largest reported number of definite *Candida* IE cases compared to non-fungal cases, there are important limitations. The data were collected prospectively, but analysis was conducted retrospectively. The number of *Candida* cases is not large enough to draw conclusions regarding treatment, and long-term mortality data were not collected.

These data represent a multi-center collaborative effort describing a large cohort of definite endocarditis cases. There appear to be distinct epidemiologic features of *Candida* IE when compared to non-fungal cases. Indications for surgical intervention are different, mortality is increased, and alternative antifungal treatment options are increasingly used for this devastating disease. Large datasets or series, despite limitations, are needed to help better define *Candida* IE.

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of amphotericin B followed by fluconazole for candidaemia in non-neutropenic patients: a randomised non-inferiority trial. Lancet 2005;366(9495):1435–1442. [PubMed: 16243088]

Appendix

ICE Registry Investigators 2007

David Gordon MBBS, FRACP, FRCPA, PhD, Uma Devi MD (Flinders Medical Centre, Adelaide, Australia);Denis Spelman MD (Alfred Hospital, Amiens, France);Jan T.M. van der Meer MD, PhD (University of Amsterdam, Amsterdam, Netherlands);Carol Kauffman MD, Suzanne Bradley MD, William Armstrong MD (Ann Arbor VA Medical Center, Ann Arbor, USA);Efthymia Giannitsioti MD, Helen Giamarellou MD,PhD (Attikon University General Hospital, Athens, Greece);Stamatios Lerakis MD FAHA, FACC, FASE, FCCP (Emory University, Atlanta, USA);Ana del Rio MD, Asuncion Moreno MD, Carlos A. Mestres MD, PhD, FETCS, Carlos Paré MD, Cristina Garcia de la Maria MD, Elisa De Lazzario BSc, Francesc Marco MD, Jose M Gatell MD, José M. Miró MD, PhD, Manel Almela MD, Manuel Azqueta MD, Maria Jesús Jiménez-Expósito MD, Natividad de Benito MD, Noel Perez MD (Hosp. Clinic - IDIBAPS: University of Barcelona, Barcelona, Spain);Benito Almirante MD, Nuria Fernandez-Hidalgo MD, Pablo Rodriguez de Vera MD, Pilar Tornos MD, Vicente Falcó MD Xavier Claramonte MD, Yolanda Armero MD (Hospital Universitari Vall d'Hebron, Barcelona, Spain);Nisreen Sidani RN, MSN, Souha Kanj-Sharara MD, FACP, Zeina Kanafani MD, MS (American University of Beirut Medical Center, Beirut, Lebanon);Annibale Raglio MD, DTM&H, Antonio Goglio MD, Fabrizio Gnecchi MD, Fredy Suter MD, Grazia Valsecchi MD, Marco Rizzi MD, Veronica Ravasio MD (Ospedali Riuniti di Bergamo, Bergamo, Italy);Bruno Hoen MD,PhD, Catherine Chirouze MD, Efthymia Giannitsioti MD, Joel Leroy MD, Patrick Plesiat MD, Yvette Bernard MD (University Medical Center of Besançon, Besançon, France);Anna Casey, Peter Lambert BSc,PhD,DSc, Richard Watkin MRCP, Tom Elliott B.M., B.S., B.Med.Sci., PhD., D.Sc., FRCPath (Queen Elizabeth Hospital, Birmingham, UK);Mukesh Patel MD, William Dismukes MD (University of Alabama at Birmingham, Birmingham, USA);Angelo Pan MD, Giampiero Caros MD (Spedali Civili - Università di Brescia, Brescia, Italy);Amel Brahim Mathiron Christophe Tribouilloy MD,PhD MD, Thomas Goissen MD (South Hospital Amiens, Bron Cedex, France);Armelle Delahaye, Francois Delahaye MD, MPH, FESC, Francois Vandenesch MD, PhD (Hopital Louis Pradel, Bron Cedex, France);Carla Vizzotti MD, Francisco M. Nacinovich MD, Marcelo Marin MD, Marcelo Trivi MD, Martin Lombardero MD (Instituto Cardiovascular, Buenos Aires, Argentina);Claudia Cortes MD, José Horacio Casabé MD (Instituto de Cardiología y Cirugía Cardiovascular, Buenos Aires, Argentina);Javier Altclas MD, Silvia Kogan MD (Sanatorio Mitre, Buenos Aires, Argentina);Liliana Clara MD, Marisa Sanchez MD (Hospital Italiano, Buenos Aires, Argentina);Anita Commerford MD, Cass Hansa MD, Eduan Deetlefs MD, Mpiko Ntsekhe MD, Patrick Commerford MD (Groote Schuur Hospital, Cape Town, South Africa);Dannah Wray MD,MHS, Lisa L. Steed PhD, Preston Church MD, Robert Cantey MD (Medical University of South Carolina, Charleston, USA);Arthur Morris MD, FRCPA, David Holland MD, David Murdoch MD,DTM&H,FRACP,FRCPA,FACTM, Katherine Graham MD, Kerry Read MD, Nigel Raymond MD, Paul Bridgman MD, Richard Troughton MD, Selwyn Lang MD, Stephen Chambers MD (Canterbury Health Laboratories, Christchurch, New Zealand);Despina Kotsanas BSc (Hons), Tony M. Korman MD (Southern Health, Clayton, Australia);Gail Peterson MD, Jon Purcell BS, Paul M. Southern, Jr. MD (UT-Southwestern Medical Center, Dallas, USA);Manisha Shah MD, Roger Bedimo MD, MS (Dallas VA Medical Center, Dallas, USA);Arjun Reddy, Donald Levine MD, Gaurav Dhar MD (Wayne State University, Detroit, USA);Alanna Hanlon- Feeney, Margaret Hannan MD, BCh BAO, MSc, MRCPath, FRCPI, Sinead Kelly MD (Mater Hospitals, Dublin, Ireland);Andrew Wang MD, Christopher H. Cabell MD, MHS, Christopher W. Woods MD,MPH, Daniel J Sexton MD, Danny Benjamin, Jr MD, MPH,PhD, G Ralph Corey MD,

Jay R McDonald MD, Jeff Federspiel, John J Engemann MD, L. Barth Reller MD, Laura Drew RN, BSN, L.B. Caram MD,Martin Stryjewski MD,MHS, Susan Morpeth MBChB, Tahaniyat Lalani MD, Vance Fowler, Jr MD,MHS, Vivian Chu MD (Duke University Medical Center, Durham, USA);Bahram Mazaheri PhD, Carl Neuerburg, Christoph Naber MD (University Essen, Essen, Germany);Eugene Athan MD, Margaret Henry BSc (Hons), PhD, Owen Harris MD (Barwon Health, Geelong, Australia);Eric Alestig MD, Lars Olaison MD,PhD, Lotta Wikstrom, Ulrika Snygg-Martin MD (Sahlgrenska Universitetssjukhuset/Östra, Goteborg, Sweden);Johnson Francis MD,DM, K Venugopal MD,DM, Lathi Nair MD,DM, Vinod Thomas MD,DM (Medical College Calicut, Kerla, India);Jaruwan Chaiworramukkun MD, Orathai Pachirat MD, Ploenchan Chetchotisakd MD, Tewan Suwanich MD (Khon Kaen University, Khon Kaen, Thailand);Adeeba Kamarulzaman MBBS, FRACP, Syahidah Syed Tamin MD (University of Malaya Medical Center, Kuala Lumpur, Malaysia);Manica Mueller Premru MD, PhD, Mateja Logar MD, PhD, Tatjana Lejko-Zupanc MD, PhD (Medical Center Ljublijana, Ljublijana, Slovenia);Christina Orezzi, John Klein MD (St. Thomas' Hospital, London, UK);Emilio Bouza MD,PhD, Mar Moreno MD,PhD, Marta Rodríguez-Créixems MD,PhD, Mercedes Marín MD, Miguel Fernández MD, Patricia Muñoz MD,PhD, Rocío Fernández, Victor Ramallo MD (Hospital General Universitario Gregorio Marañón, Madrid, Spain);Didier Raoult MD,PhD, Franck Thuny MD, Gilbert Habib MD, FACC, FESC, Jean-Paul Casalta MD, Pierre-Edouard Fournier MD (Faculté de Médecine de Marseille, Marseille, France);Natalia Chipigina PhD, Ozerecky Kirill MD, Tatiana Vinogradova MD, PhD, Vadim P. Kulichenko PhD (Russian Medical State University, Moscow, Russia);O.M. Butkevich PhD (Learning Medical Centre of Russian Presidential Affairs Government, Moscow, Russia);Christine Lion MD, Christine Selton-Suty MD, Francois Alla MD, PhD, Hélène Coyard, Thanh Doco-Lecompte MD (CHU Nancy-Brabois, Nancy, France);Diana Iarussi MD, Emanuele Durante-Mangoni MD, PhD, Marie Françoise Tripodi MD, Riccardo Utili MD (II Università di Napoli, Naples, Italy);A. Sampath Kumar MD, Gautam Sharma MD (All India Institute of Medical Sciences, New Delhi, India);Stuart A. Dickerman MD (New York University Medical Center, New York, USA);Alan Street, Damon Peter Eisen MBBS, MD, FRACP, Emma Sue McBryde MBBS, FRACP, PhD, Leeanne Grigg (Royal Melbourne Hospital, Parkville, Australia);Elias Abrutyn MD (Drexel University College of Medicine, Philadelphia, USA);Christian Michelet MD, PhD, Pierre Tattevin MD, Pierre Yves Donnio PhD (Pontchaillou University, Rennes, France);Claudio Querido Fortes MD (Hospital Universitario Clementino Fraga Filho/UFRJ, Rio de Janeiro, Brazil);Jameela Edathodu MRCP, Mashael Al-Hegelan MD (King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia);Bernat Font MD, Ignasi Anguera MD, PhD, Joan Raimon Guma MD (Hospitál de Sabadell, Sabedell, Spain);M Cereceda MD, Miguel J. Oyonarte MD, Rodrigo Montagna Mella Md (Hospital Clinico Universidad de Chile, Santiago, Chile);Patricia Garcia MD, Sandra Braun Jones MD (Hosp. Clínico Pont. Universidad Católica de Chile, Santiago, Chile);Auristela Isabel de Oliveira Ramos MD (Instituto Dante Pazzanese de Cardiologia, São Paulo, Brazil);Marcelo Goulart Paiva MD, Regina Aparecida de Medeiros Tranchesi MD (Hospital 9 de Julho, São Paulo, Brazil);Lok Ley Woon BSN, Luh-Nah Lum BSN, Ru-San Tan MBBS, MRCP (National Heart Centre, Singapore, Singapore);David Rees MD, Pam Kornecny MD, Richard Lawrence MD, Robyn Dever MD (St. George Hospital, Sydney, Australia);Jeffrey Post MD, Phillip Jones MD, Suzanne Ryan MHSc, GCDM (The University of New South Wales, Sydney, Australia);John Harkness MD, Michael Feneley MD (St. Vincent's, Sydney, Australia);Ethan Rubinstein MD, LL.B, Jacob Strahilewitz MD (Tel Aviv University School of Medicine, Tel Aviv, Israel);Adina Ionac MD,PhD, Cristian Mornos MD, Stefan Dragulescu MD,PhD (Victor Babes University of Medicine and Pharmacy, Timisoar, Romania);Davide Forno MD, Enrico Cecchi MD, Francesco De Rosa MD, Massimo Imazio MD, FESC, Rita Trinchero MD (Maria Vittoria Hospital, Torino, Italy);Franz Wiesbauer MD, Rainer Gattringer MD (Vienna General Hospital, Vienna, Austria);Ethan Rubinstein MD,LLB, Greg Deans MD (University of Manitoba, Winnipeg, Canada);Arjana Tambic Andrasevic MD, PhD, Bruno Barsic MD, PhD, Igor Klinar MD, Josip Vincelj MD, PhD, FESC,

Suzana Bukovski MD, Vladimir Krajinovic MD (Univ. Hospital for Infectious Diseases, Zagreb, Croatia);

Table 1

Characteristics of patients with *Candida* and non-fungal endocarditis from the International Collaboration of endocarditis (ICE) Database (n=2749)

Characteristic	Level	*Candida* n =33(%)	Non-fungal n=2716 (%)	*P*-value[a]
Age	Mean ± SD	54.9 ±18.95	56.7 ±17.84	0.58
Gender	Male	17(51.5)	1844(67.9)	0.04
	Female	16(48.5)	859 (31.6)	
	Missing	0(0.5)	14 (0.5)	
Hemodialysis	Yes	2 (6)	218(8)	0.68
	No	31(94)	2259(83.2)	
	Missing	0	17(0.6)	
Diabetes	Yes	7(21.2)	440(16.2)	0.45
	No	26(78.8)	2285(83.1)	
	Missing	0	17(0.6)	
Current IVDA	Yes	4(12.1)	262(9.7)	0.60
	No	28(84.9)	2449(89)	
	Missing	1(3)	33(1.2)	
HIV	Yes	3(9)	54(2)	0.005
	No	30(90.9)	2639(96.8)	
	Missing	0	32(1.2)	
Malignancy	Yes	2(6)	227(8.4)	0.63
	No	31(94)	2480(91)	
	Missing	0	9(0.3)	
Chronic Immunosuppressives	Yes	5(15.2)	156(5.7)	0.023
	No	28(84.9)	2530(93)	
	Missing	0	30(1.1)	
Congenital Heart Disease	Yes	4(12.1)	300(11)	0.82
	No	27(81.8)	2294(84.5)	
	Missing	2(6)	122(4.5)	
Type of IE	Native	15(45.5)	1875(69)	0.0005
	Prosthetic	16(48.8)	533(19.6)	
	Other	2(6)	169(6.2)	
	Missing	0	139(5.1)	
Recent Dental Procedures	Yes	1(3)	216(8)	0.27
	No	27(81.8)	2011(741)	
	Missing	5(15.2)	489(18)	
CABG[b]	Yes	2(22.2)	18(3.7)	0.007
	No	7(77.8)	447(92.4)	
	Missing	0	19(3.9)	
Chronic Indwelling Catheter	Yes	3(9.1)	132(4.9)	0.26
	No	30(90.9)	2566(94.5)	
	Missing	0(0)	18(0.7)	
Short term Indwelling Catheter	Yes	7(21.2)	119(4.4)	<0.0001

Characteristic	Level	*Candida* n =33(%)	Non-fungal n=2716 (%)	*P*-value[a]
	No	26(78.8)	2567(94.5)	
	Missing	0(0)	24(0.88)	
Endocavitary Device[c]	Yes	6(18.2)	305(11.2)	0.65
	No	27(81.8)	2411(88.8)	
	Missing	0	19(3.9)	
Previous IE	Yes	7(21.2)	213(7.8)	0.005
	No	26(78.8)	2502(92.1)	
	Missing	0	1(0.04)	
Healthcare Associated	Yes	17(51.5)	702(25.8)	0.0009
	No	16(48.5)	2014(74.1)	

[a] P-values were obtained by Chi Square or Fischer's exact methods.

[b] Among patients who had an invasive procedure within 60 days prior to onset of symptoms

[c] Refers to pacemakers, intracardiac defibrillators, or other.

SD=standard deviation; IVDA=intravenous drug abuse; IE=infective endocarditis; CABG=coronary artery bypass grafting

Table 2

Clinical Findings of Patients with *Candida* and Non-Fungal Endocarditis

Clinical Finding	Level	*Candida* n =33(%)	Non-fungal n=2716(%)	*P* Value[a]
Time since clinical manifestation	<1 month	22(66.7)	2046 (75.3)	0.41
	>1 month	9(27.3)	602(22.2)	
	Missing	2(6)	689(2.5)	
Evidence of IE on Exam	Yes	25(75.6)	2272(83.6)	0.15
	No	7(21.2)	344(12.7)	
	Missing	1(3)	100(3.7)	
Fever > 38.0° C[b]	Yes	23(92)	2147(94.4)	0.42
	No	2(8)	104(5.8)	
	Missing	0	21(0.9)	
Osler's Nodes[b]	Yes	2(8)	73(3.21)	0.19
	No	23(92)	2178(95.9)	
	Missing	0	21(0.9)	
Janeway Lesions[b]	Yes	2(8)	116(5.1)	0.52
	No	23(92)	2135(94)	
	Missing	0	21(0.9)	
Roth spots[b]	Yes	2(8)	46(2)	0.04
	No	23(92)	2205(97)	
	Missing	0	21(0.9)	
Vascular Embolic Event[b]	Yes	6(24)	429(18.9)	0.53
	No	19(76)	1822(80.2)	
	Missing	0	21(0.92)	
Splenomegaly[b]	Yes	3(12)	265(11.7)	0.97
	No	22(88)	1986(87.4)	
	Missing	0	21(0.92)	
New Murmur	Yes	10(30)	1043(38)	0.15
	No	19(57.6)	1134(41.8)	
	Missing	4(12)	539(19.9)	
Intracranial Hemorrhage	Yes	2(6)	111(4)	0.56
	No	30(90.9)	2535(93.3)	
	Missing	1(3)	70(2.6)	
Intracranial Hemorrhage	Yes	5(15.2)	248(9.1)	0.22
	No	27(8.18)	2408(88.7)	
	Missing	1(3)	12(0.59)	
TTE Evidence of IE[c]	Yes	17(68)	1448(64.5)	0.96
	No	8(32)	667(29.7)	
	Missing	2(6)	75(2.76)	
TEE Evidence of IE[c]	Yes	24(96)	1757(90.7)	0.76
	No	1(4)	100(5.1)	
	Missing	2(6)	94(3.7)	

Clinical Finding	Level	*Candida* n =33(%)	Non-fungal n=2716(%)	*P* Value[a]
Surgery this episode	Yes	15(45.5)	1301(47.9)	0.76
	No	18(54.5)	1403(51.2)	
	Missing	0	12(0.44)	
Indications for Cardiac Surgery				
CHF	Yes	2(13.3)	554(42.6)	0.02
	No	13(86.7)	735(56.5)	
	Missing	0	12(0.9)	
Embolization	Yes	6(40)	257(19.8)	0.05
	No	9(60)	1032(79.3)	
	Missing	0	12(0.9)	
Persistent positive blood cx.	Yes	5(33.3)	129(9.9)	0.003
	No	10(67)	1160(89.2)	
	Missing	0	12(0.9)	
Myocardial abscess	Yes	7(46.7)	289(22.2)	0.026
	No	8(53.3)	1000(76.9)	
	Missing	0	12(0.9)	
Valvular regurgitation	Yes	6(40)	885(68)	0.018
	No	9(60)	404(31)	
	Missing	0	12(0.9)	
Vegetation	Yes	6(40)	639(49.1)	0.46
	No	9(60)	651(50)	
	Missing	0	11(0.9)	

[a] P-values were obtained by Chi Square or Fisher's exact methods.

[b] Includes patients who had evidence of IE on history or physical exam (n=25 for Candida group and N=2272 for non-fungal group)

[c] Not all patients had echocardiography.

TTE=transthoracic echocardiography; TEE=tranesophageal echocardiography; CHF=congestive heart failure; IE=infective endocarditis; Cx=culture.

Table 3

Complications and Outcomes of Patients with *Candida* and Non-fungal endocarditis

Characteristic	Level	*Candida* n=33 (%)	Non-fungal n =2716 (%)	*P* Value[a]
Stroke	Yes	4(12.1)	450(16.6)	0.51
	No	28(84.8)	2213(81.5)	
	Missing	1(3)	53(2)	
Embolization	Yes	10(30.3)	592(21.8)	0.23
	No	22(66.7)	2053(75.6)	
	Missing	1(3)	71(2.6)	
CHF	Yes	8(24.2)	856(31.5)	0.44
	No	23(69.7)	1794(66)	
	Missing	2(6)	66(2.4)	
Persistent Positive Blood Cx	Yes	13(39.4)	238(8.8)	<0.001
	No	19(57.6)	2397(88.3)	
	Missing	1(3)	81(3)	
Mortality at Discharge	Yes	10(30.3)	464(17)	0.046
	No	23(69.7)	2243(82.6)	
	Missing	0	9(0.33)	
Mortality (with surgery)[b]	Yes	5(33.3)	179(13.8)	0.030
	No	10(66.7)	1120(86.1)	
	Missing	0	2(0.2)	
Mortality (without surgery)[b]	Yes	5(27.8)	285(20.3)	0.83
	No	13(72.2)	1117(79.6)	
	Missing	0	1(0.1)	

[a] P-values were obtained by Chi Square and Fisher's exact methods

[b] Refers to cardiothoracic surgery. Mortality determined at time of discharge.

CHF=congestive heart failure. Cx=culture.

Table 4

Treatment for 27 patients with *Candida* IE

Patient[1]	Organism	Therapy	Surgery	Outcome[2]
1	*C. parapsilosis*	AmB	Yes	Alive
2	*C. albicans*	FLU then CASPO	No	Dead
3	*C. albicans*	CASPO then FLU	Yes	Alive
4	*C. parapsilosis*	FLU/CASPO[3]	No	Alive
5	*C. glabrata*	FLU then CASPO	No	Alive
6	*C. albicans*	FLU	No	Alive
7	*C. glabrata*	AmB	No	Alive
8	*C. tropicalis*	AmB	Yes	Dead
9	*C. albicans*	AmB then FLU	No	Dead
10	*C. glabrata*	CASPO + Lipid AmB followed by CASPO[4]	No	Alive
11	*C. parapsilosis*	AmB/CASPO[3]	Yes	Alive
12	*C. glabrata*	CASPO	No	Alive
13	*C. parapsilosis*	AmB	Yes	Alive
14	*C. albicans*	Lipid AmB then FLU	Yes	Alive
15	*C. albicans*	FLU	No	Dead
16	*C. albicans*	FLU	No	Alive
17	*C. parapsilosis*	CASPO	Yes	Dead
18	*C. glabrata*	AmB	No	Alive
19	*C. albicans*	AmB	No	Dead
20	*C. albicans*	AmB	Yes	Alive
21	*C. parapsilosis*	AMB then FLU	No	Alive
22	*C. albicans*	FLU + 5-FC	Yes	Alive
23	*C. tropicalis*	AmB	No	Alive
24	*C. parapsilosis*	CASPO then FLU	No	Alive
25	*C. tropicalis*	Lipid AmB	Yes	Dead
26	*C. albicans*	AmB then VORI	Yes	Alive
27	*C. albicans*	AmB	No	Dead

[1] Only 27 patients had treatment data available

[2] Outcome at time of hospital discharge

[3] Treatment data other than drugs received were unavailable

[4] Patient received 1 month of VORI for suppressive therapy after an initial 11 weeks of treatment with CASPO and lipid AmB. Because of toxicity with VORI, CASPO was administered for an additional 8 weeks.

AmB= amphotericin B; Lipid AmB= liposomal AmB; CASPO=caspofungin; FLU=fluconazole; 5-FC=flucytosine; VORI=voriconazole